Alzheimer's disease Epidemiology, Risk Factors and Global Burden

Lefkos T Middleton, MD, FRCP

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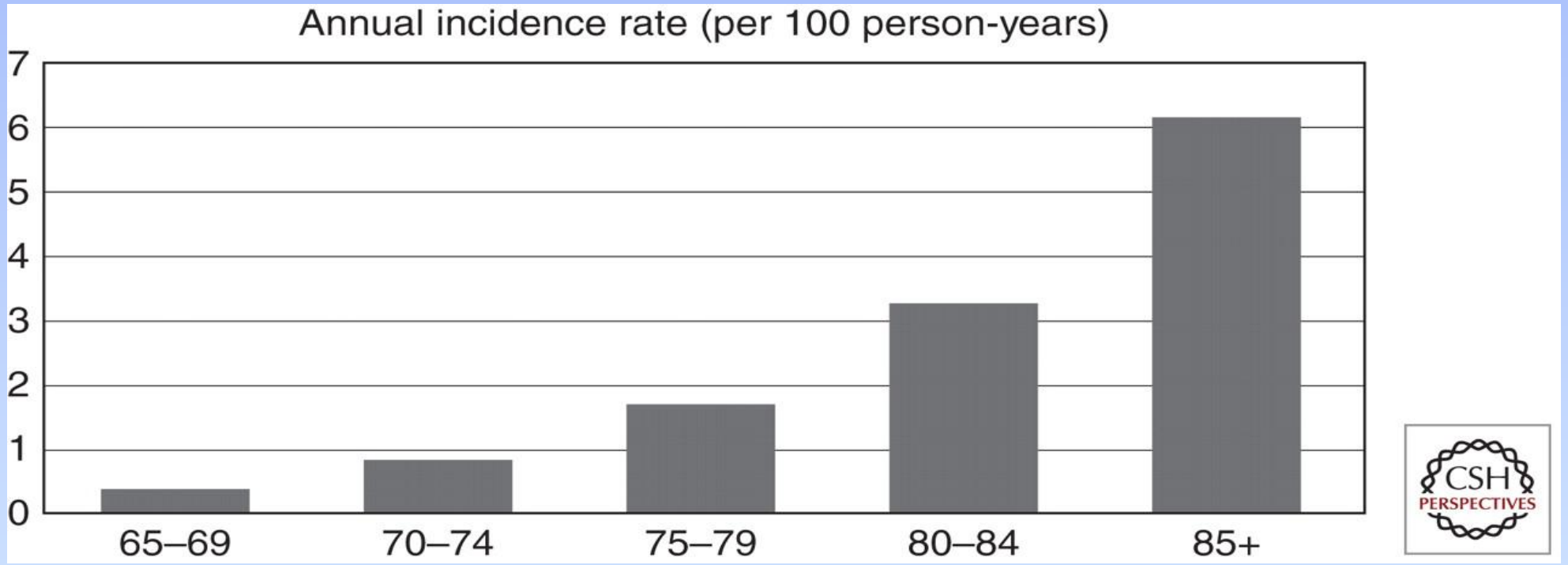
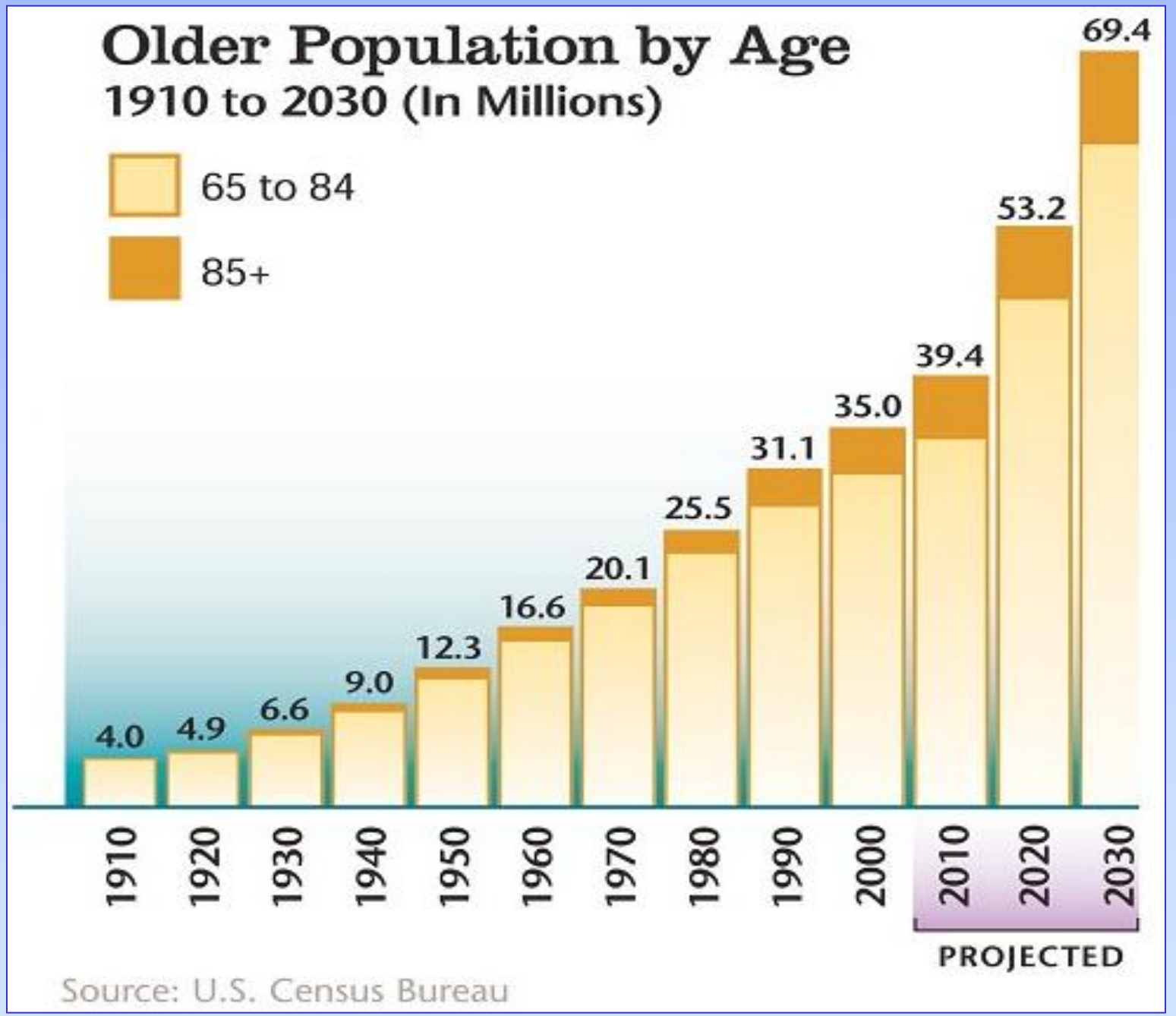
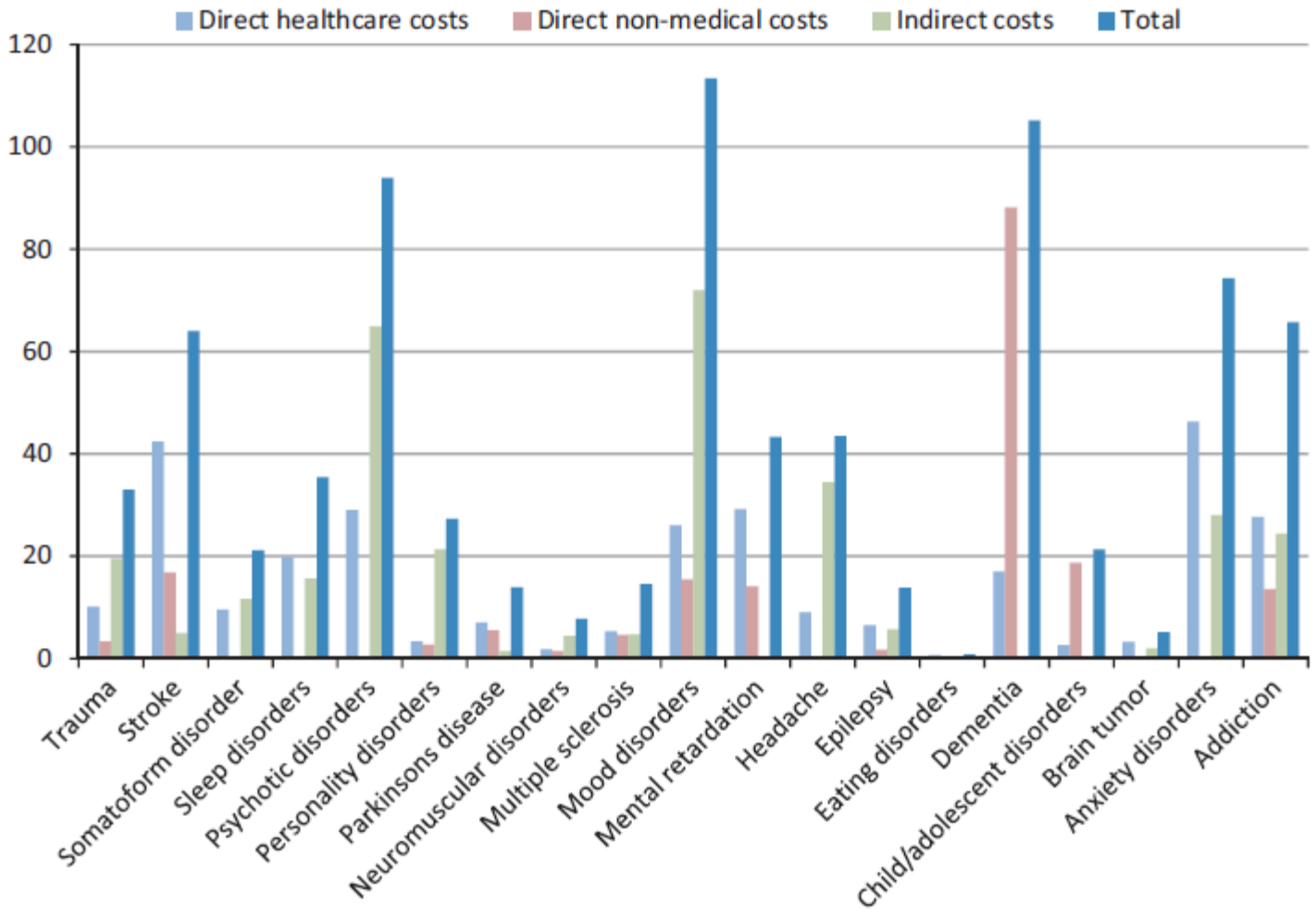
The annual incidence rate (per 100 person-years) for Alzheimer disease.



Mayeux R , Stern Y Cold Spring Harb Perspect Med 2012;2:a006239


Older Population by Age
1910 to 2030 (In Millions)
65 to 84
85+
4.0
4.9
6.6
9.0
12.3
16.6
20.1
25.5
31.1
35.0
39.4
53.2
69.4
1910
1920
1930
1940
1950
1960
1970
1980
1990
2000
2010
2020
2030
PROJECTED
Source: U.S. Census Bureau



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Current costs of dementia care in World bank countries

Table 1 Aggregated costs in different World Bank income groups (billions US$)

	Number of people with dementia	Informal care (all ADL)	Direct costs		Total costs	Percent of GDP
			Medical	Social		
Low income	5036979	2.52	1.23	0.62	4.37	0.24%
Lower middle income	9395204	18.90	6.74	3.57	29.21	0.35%
Upper middle income	4759025	13.70	10.44	8.35	32.49	0.50%
High income	16367508	216.77	78.00	243.14	537.91	1.24%
All	**35558717**	**251.89**	**96.41**	**255.69**	**603.99**	**1.01%**

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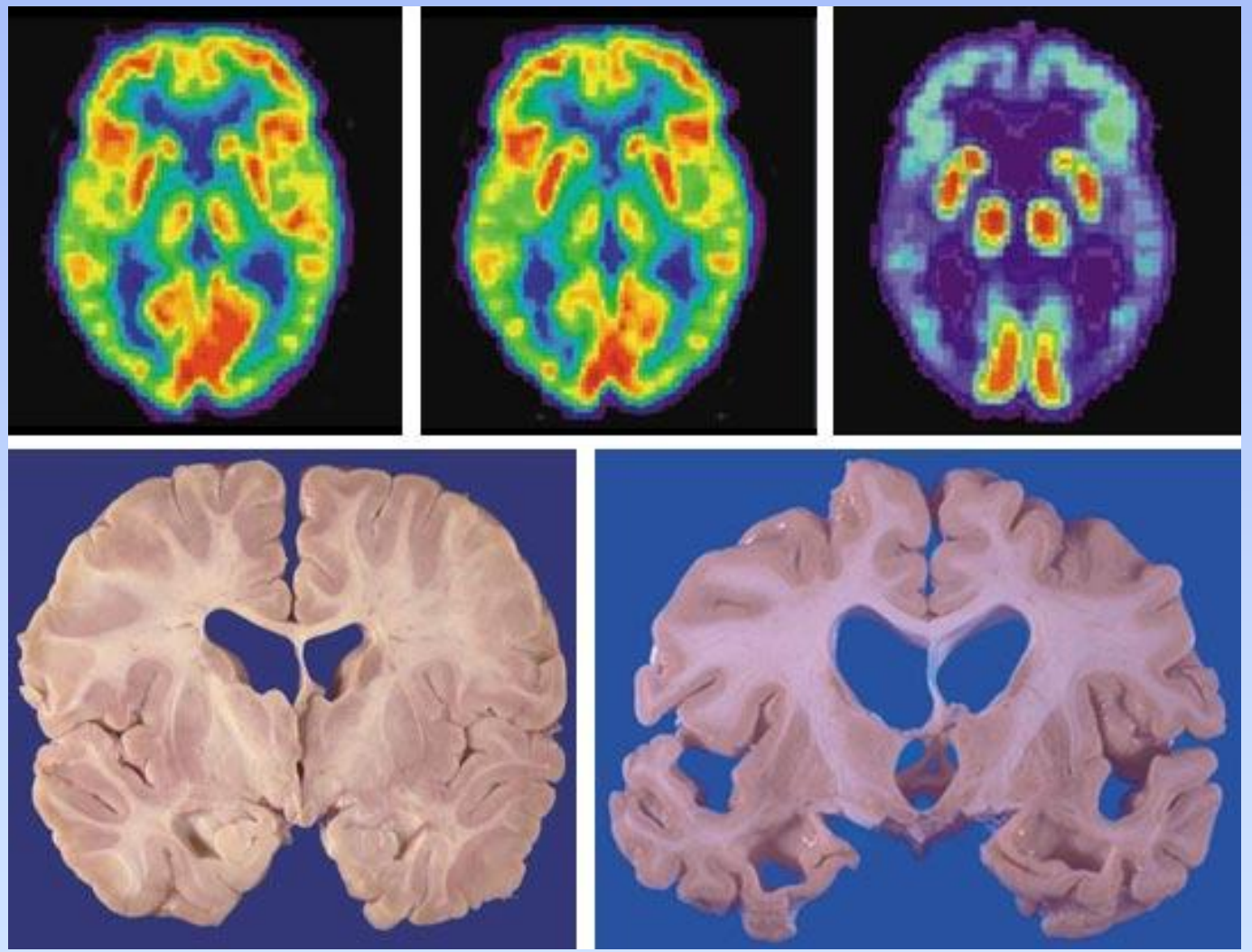
Late Onset Dementias

- **Alzheimer's Disease: Most common > 70%**
- **Lewy Body Dementias – linked with Parkinson's disease**
- **Vascular Dementia**

Brain Atrophy in Alzheimer's disease



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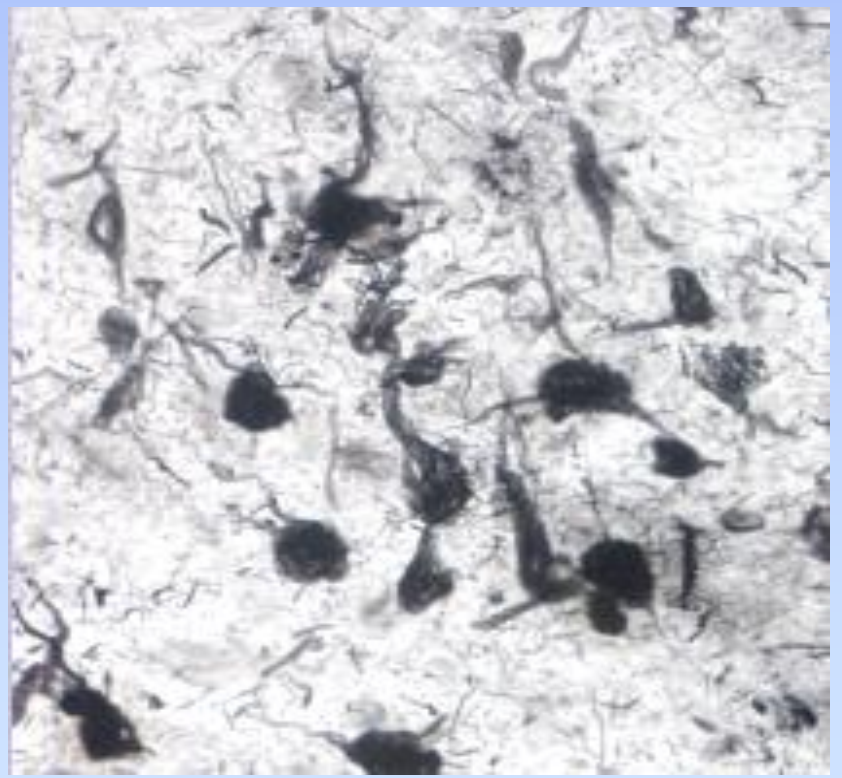
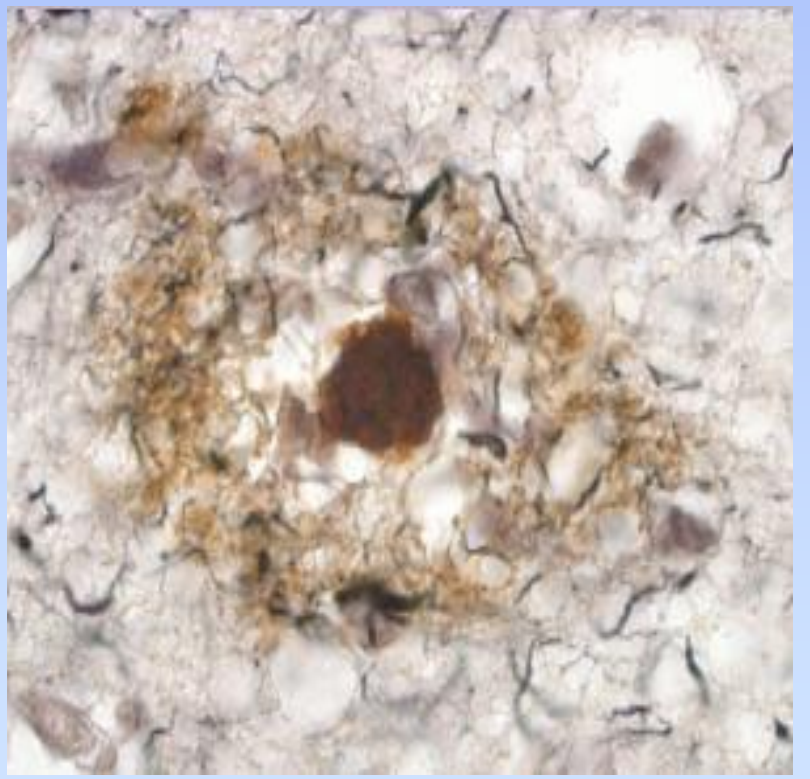
ARMD New Post Genetic classification

1.	**Proteins of the extracellular matrix**	
	laminin α2	(MDC1A)
	collagen 6A1, A2, A3	(UCMD)
	integrin α7	(ITGA7)
2.	**Transarcolemmal proteins**	
	dystrophin	(DMD-BMD)
	α, β, γ, δ sarcoglycans	(LGMD2C-2D-2E-2F)
	caveolin	(LGMD1C)
	dysferlin	(LGMD2B)
3.	**Sarcomeric proteins**	
	myotilin	(LGMD1A)
	dysferlin	(LGMD2G)
	titin	(LGMD2H)
4.	**Nuclear proteins**	
	emerin	(XL-EDMD)
	lamin A/C	(AD-EDMD/LGMD1B)
	PAB2	(OFMD)
5.	**Proteins with enzymatic activity**	
	calpain	(LGMD2A)
	fukutin	(FCMD)
	fukutin-related protein	(MDC1C/ LGMD2I)
	POMGnT1	(MEB)
6.	**Cytoskeletal proteins**	
	plectin	(MD+ epid.bull)

Neurofibrillary tangles



Neuritic plaques



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A new era in AD research from new genetic discoveries

early onset- familial- AD	**Locus**
ß-Amyloid precursor (ßAPP)	*Chromosome 21 (1991)*
Presenilin-1	*Chromosome 14 (1995)*
Presenilin-2	*Chromosome 1 (1995)*

late onset- sporadic	
ApoE (risk factor)	*Chromosome 19 (1993)*
TOMM40- IVS6 PolyT	*„ (2011)*

www. Alzgene.org: > 40 candidate genes reported (2011)

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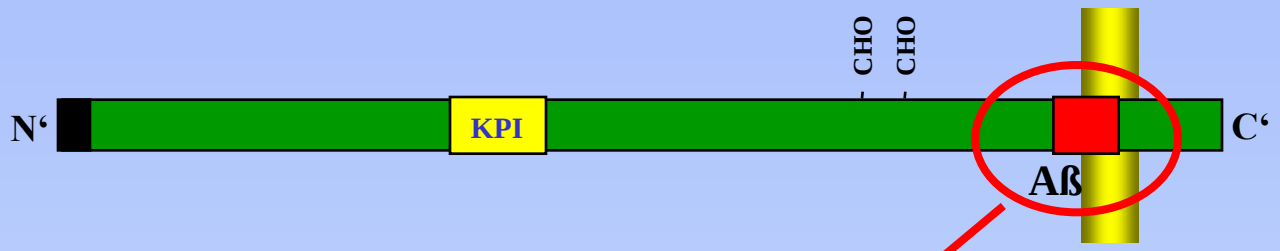
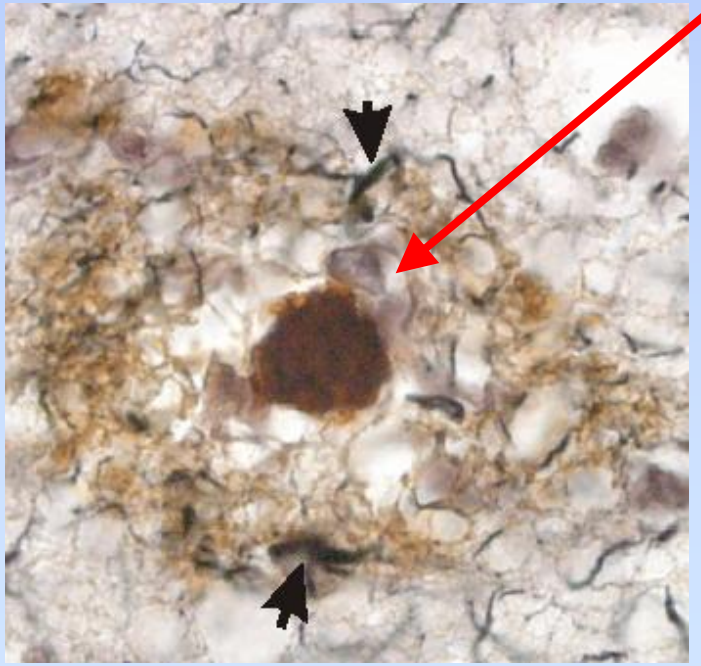
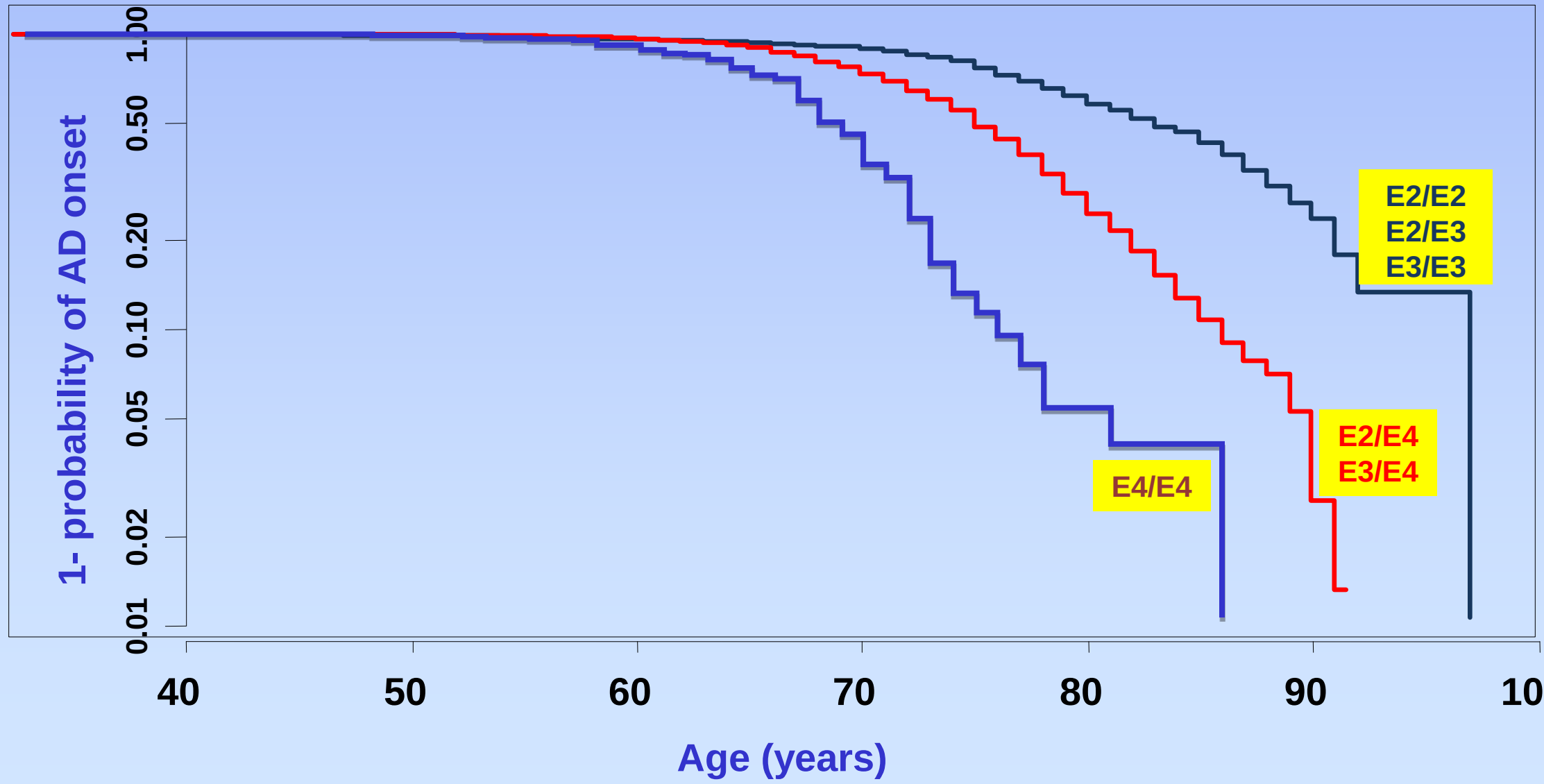
The ß-amyloid precursor protein



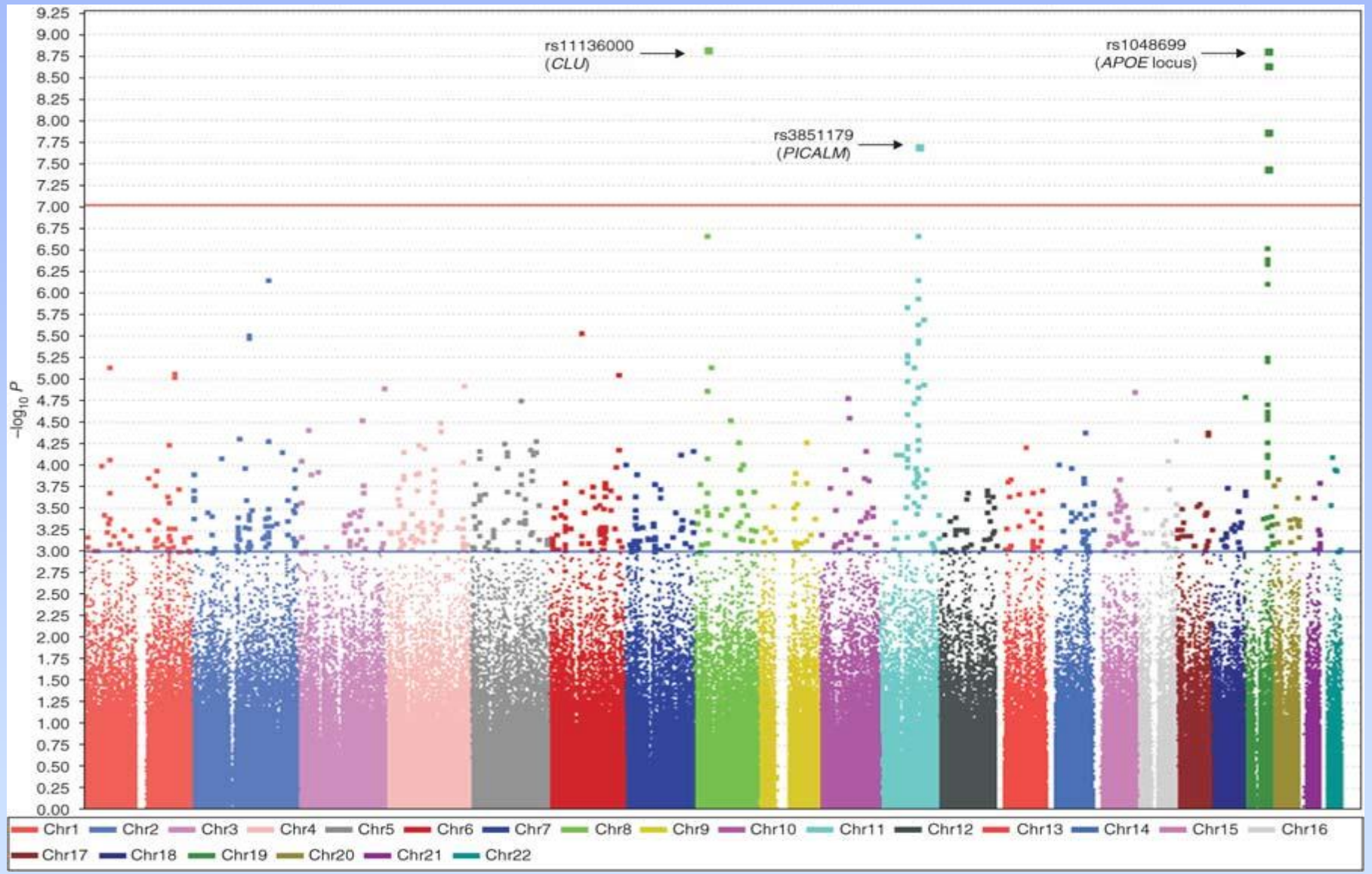


Kaplan-Meier survival curves
AD onset by age and APoE 2,3,4 alleles

(Hao et al, Arch Neurol 2007)

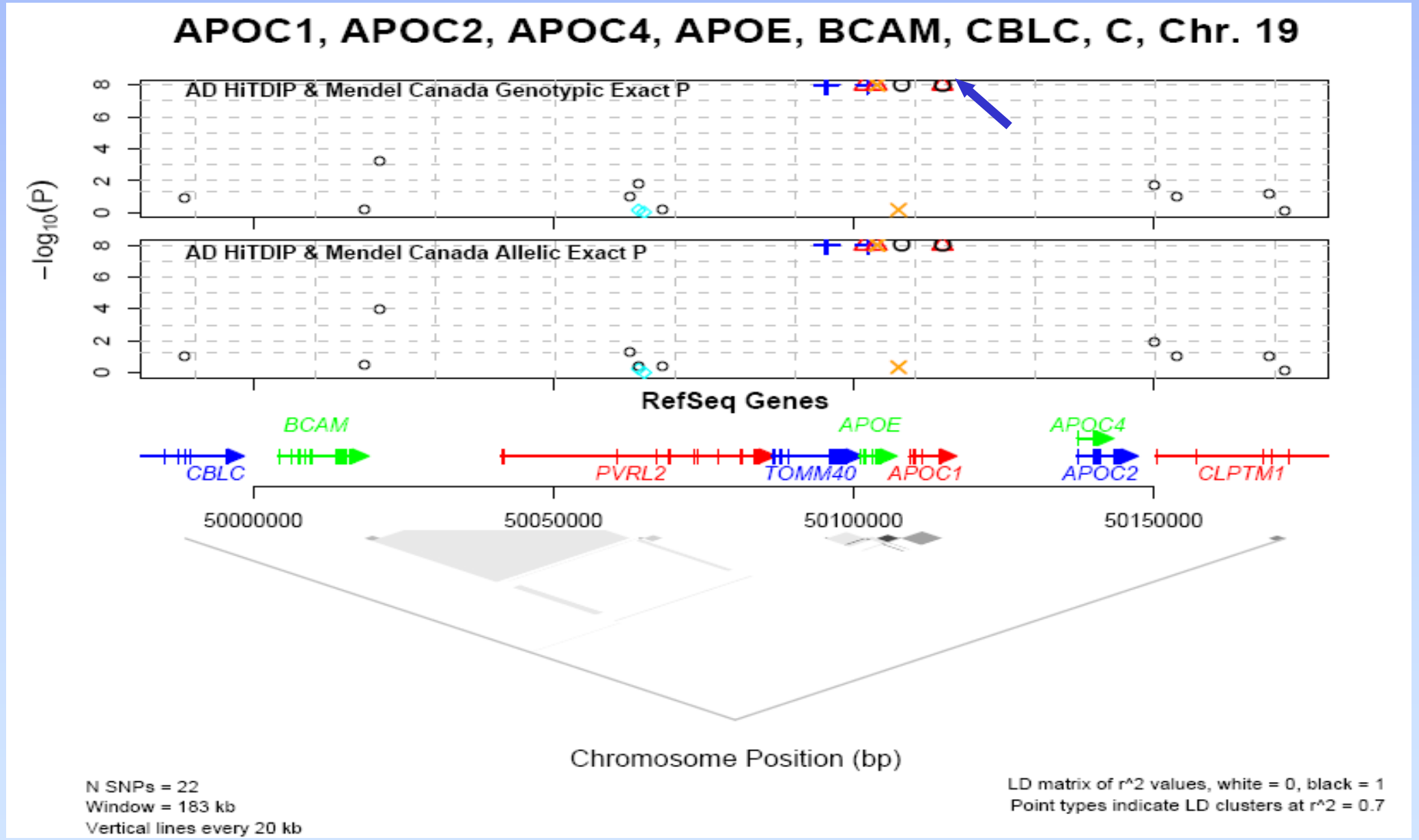


Scatterplot of chromosomal position (*x* axis) against -log10 GWAS *P* value (*y* axis)



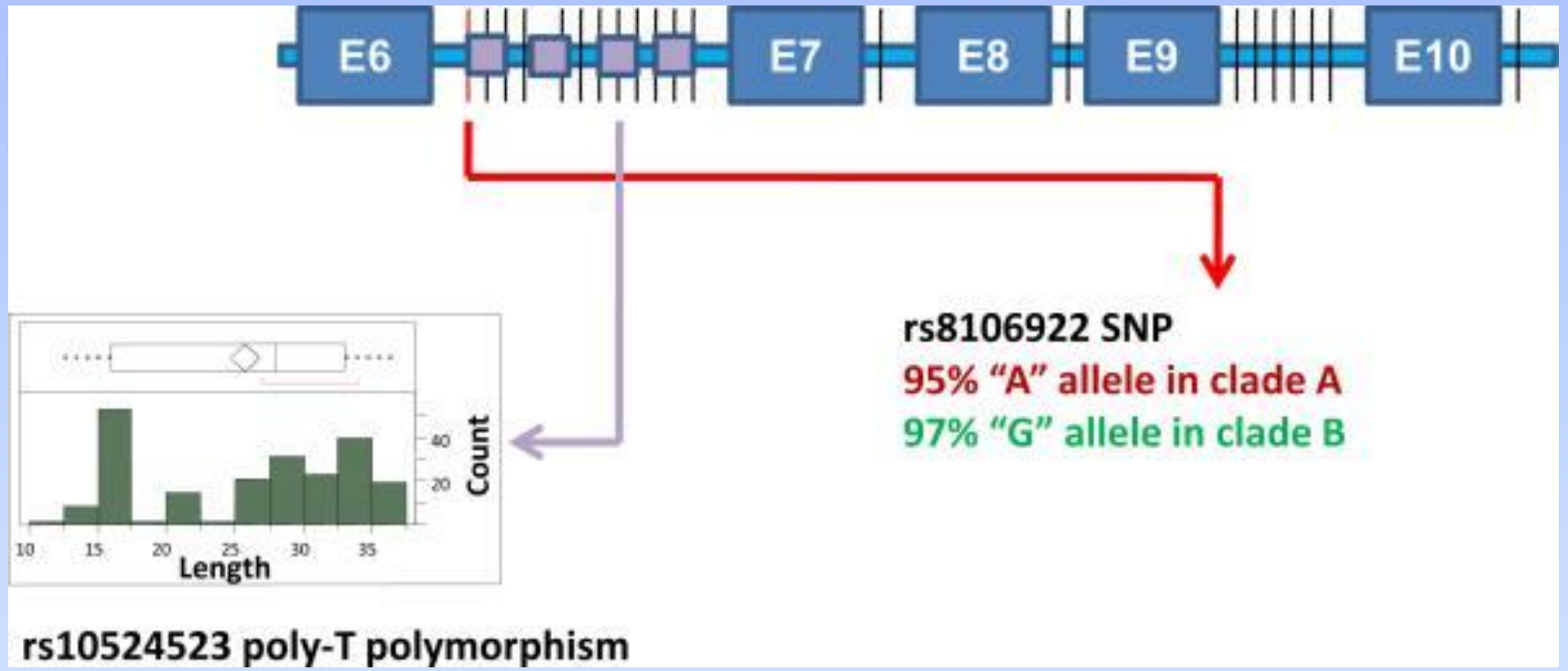
Harold et al. Nat Genet. 2009 Oct; 1088 - 1093 (2009)

APOE in strong LD with TOMM40 in AD



TOMM40 is a key susceptibility gene for AD

Lutz et al, 2011



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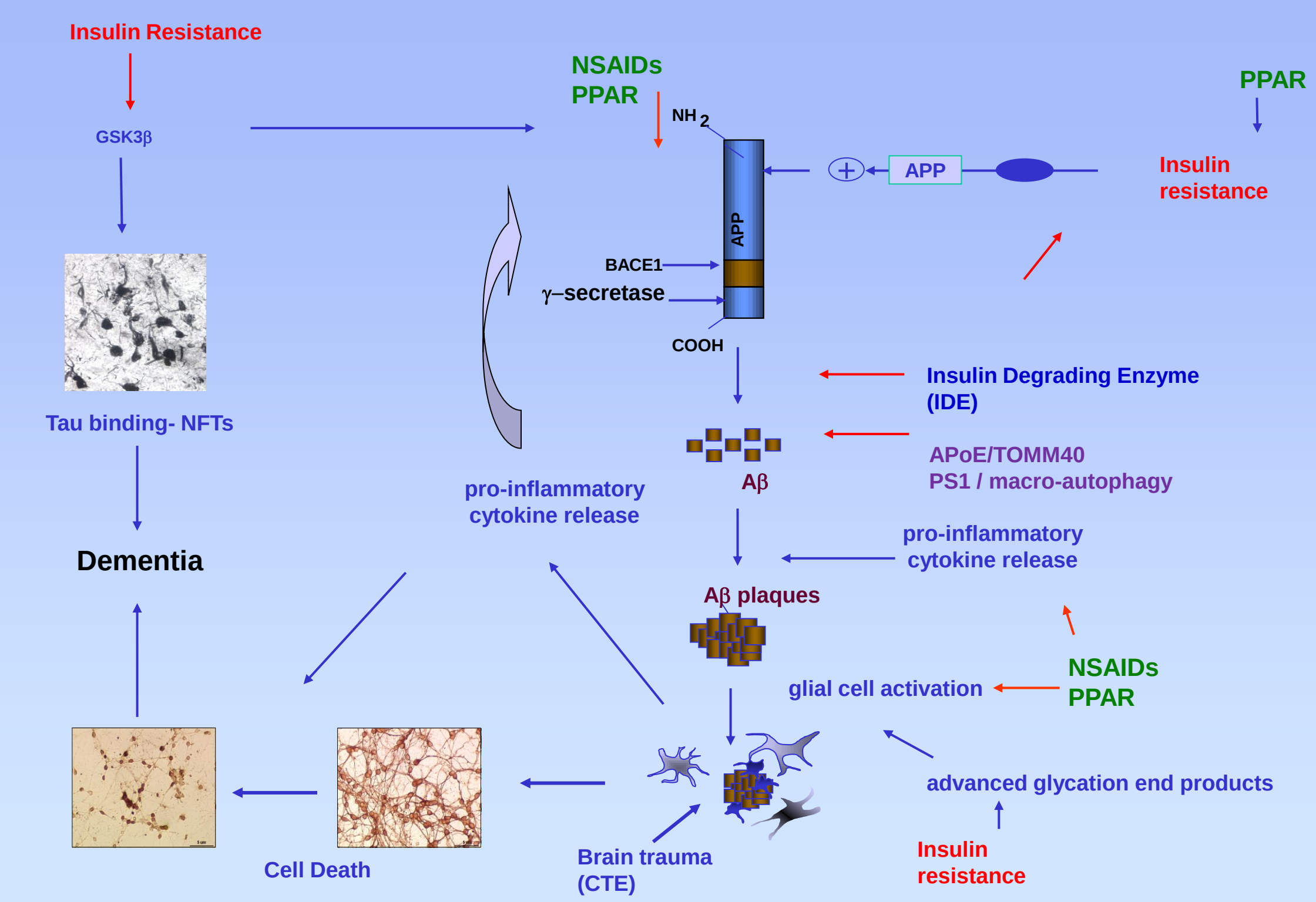
Insulin Resistance
GSK3β
NSAIDs
PPAR
NH 2
APP
PPAR
Insulin
resistance
BACE1
γ–secretase
COOH
Tau binding- NFTs
Insulin Degrading Enzyme
(IDE)
APoE/TOMM40
PS1 / macro-autophagy
Aβ
pro-inflammatory
cytokine release
pro-inflammatory
cytokine release
Dementia
Aβ plaques
NSAIDs
PPAR
glial cell activation
advanced glycation end products
Cell Death
Brain trauma
(CTE)
Insulin
resistance

Possible Role of ApoE and TOMM40 in AD

- **APoE 4 & TOMM40 polyT increase the risk of AD, lower AOO but carrying the risk alleles does not necessarily lead to dementia!**

- **APoE**

  - binds to Aβ40-42, facilitates their ***proteolytic degradation*** and **clearance across the blood brain barrier**

  - APoE4 may strongly influence Aβ fibrinogenesis and may facilitate oligomer- Aβ40-42 neurotoxicity *(Jiang et al, 2008)*

  - The lipid and receptor binding regions of ApoE4 fragments and TOMM40 may also act in concert to cause ***mitochondrial dysfunction*** and hypo-mobility with resulting neurotoxicity *(Chang et al, 2007)*

  - Integrity of blood brain barrier (BBB)

- **TOMM40**

  - part of the protein import machinery of mitochondria (*P. Dolezal et al, 2006)*

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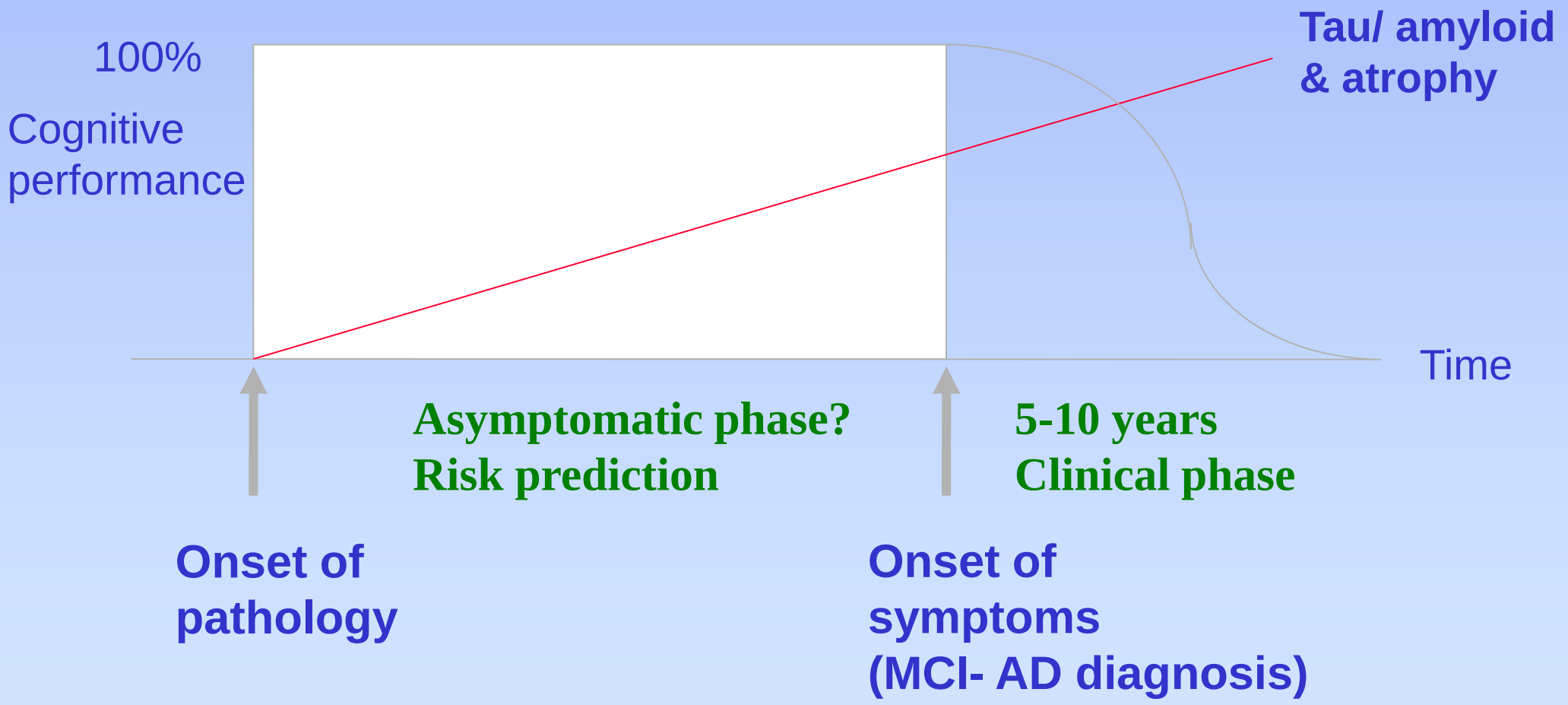
Alzheimer disease-related lesions begins in middle age

Kok et al, Ann Neurol, 2009

- 603 autopsies in Tampere Finland from unrelated / unexpected deaths, with no history of AD & related illnesses, aged 0-93
- 30 % had APs, and 42% had NFTs – from age 30, reaching 100% in oldest; F>M
- **40 % of APoE4 carriers at age 50-59 had APs (compared to 8 % in non-carriers)**

Theoretical disease pattern of cognitive decline in Alzheimer's disease



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Microglial Activation (MA) in AD

- MA is an **early** event, preceeding inclusion formation in AD-Tg mice [APP and Tau] (*Yoshimaya et al, 2007, El Khoury et al, 2008)*
- Early in the disease, MA may be **protective** via clearance of Aß, while glia form a protective barrier between Aß and neurons (*Wyss- Coray, 2006; Rossner et al, 2005; Maragakis et al, 2006)*
- In late stages, MA may become **detrimental** through chronic release of cytokines and khemokines (*Hickman et al, 2008)*
- Astrocytes may prolong inflammation and contribute to nitric oxide (NO)- mediated **neurotoxicity**

(Sastre et al, 2006; Heneka et al, 2007)

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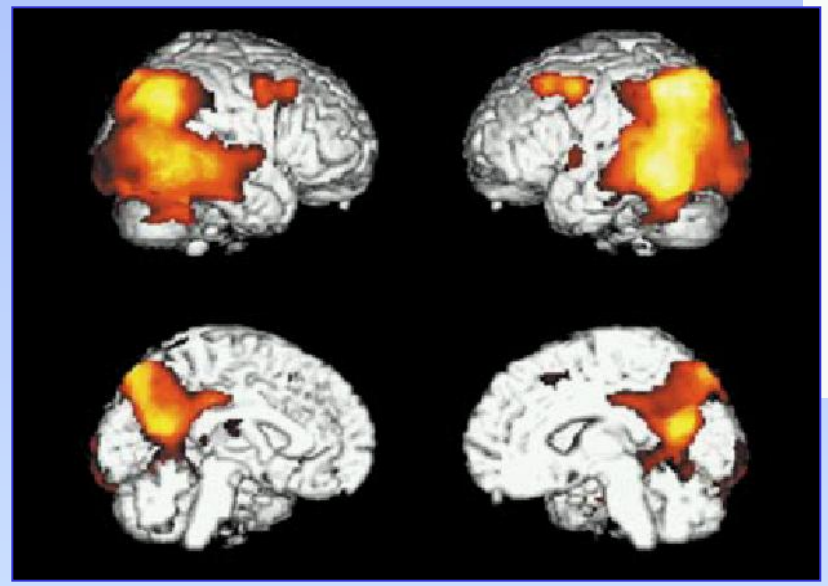
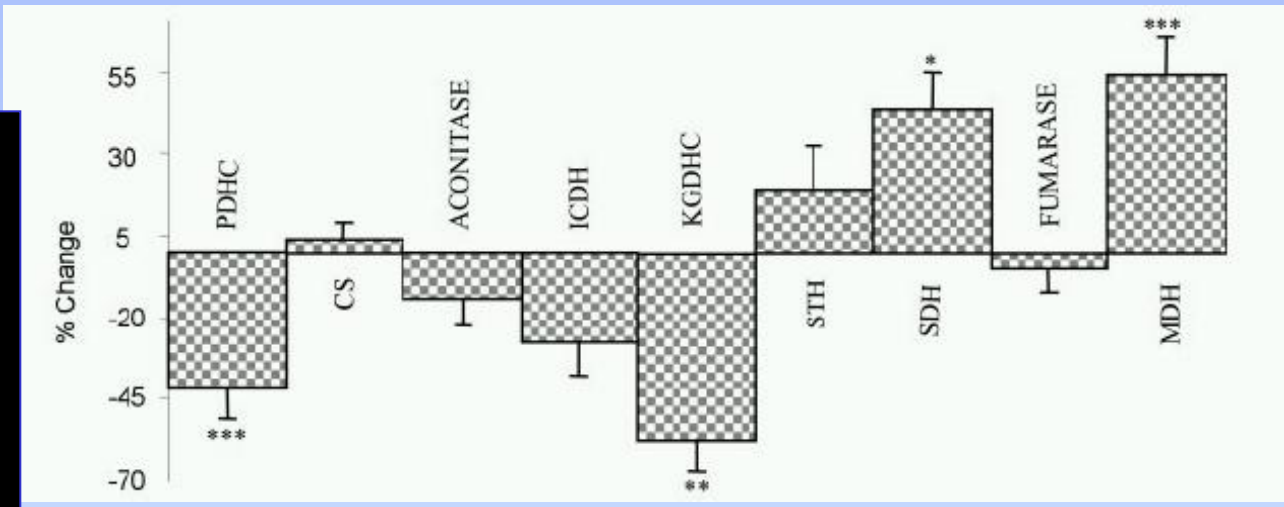
Oxidative dysfunction in AD





- **FDG PET: oxidative metabolism is reduced regionally in AD**
- **Decreased expression of rate-limiting enzymes for mitochondria in AD**

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Diabetes/ Insulin Resistance in AD

- Twofold increased risk for AD. 2D,
- *Insulin resistance* has been linked to AD because hyperinsulinemia competes for IDE and thus disrupts Aβ clearance
- Also through increased intracellular production of glycation products which can be neurotoxic/ pro-inflammatory
- Insulin and insulin-like growth factor-1 stimulation may promote tau phosphorylation / binding to microtubules in neurofibrillary tangles
- Obesity, insulin resistance and T2D are also associated with abnormal cytokine production and activation of inflammation signal pathways *(Welton et al, 2005; Hotalmisligi, 2006)*
- ***Intra-nasal injection of Insulin (Reger et al, 2008) now in phase II (NIH funded); several trials of Risglitazone and Pioglitazone***

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In AD, normal amounts of Insulin are inadequate to produce a normal Insulin response in brain regions

Hence, AD has been termed as T3D…!

'sciencedaily.com', 2008

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Single dietary components and Risk of AD

- Variable usually conflicting results
- Risk Increased by saturated fatty acids (SFAs) and cholesterol
- Risk decreased (???) by PUFAs, fish, vitamins and flavonoids, moderate consumption on alcohol & coffee drinking…

Healthy Diet and Risk of AD

- **WHICAP Study (NYC): Higher adherence to a Mediterranean diet associated with a decreased risk of AD and of mortality** *(Scarmeas et al, 2006, Gu et al, 2010)*
- **Three City Study (France): Mediterranean diet asociated to slower decline but not to risk of AD** *(Feart et al, 2009)*
- **CAIDE (Finland): healthy diet at mid-life associated to a decreased risk of AD in late life** *(Eskelinen et al, 2011)*

The Smoking Saga in AD

- Associated with reduced risk in PD
- Early C/C studies showed possible similar effect in AD
- But recent longitudinal and meta-analyses showed RR at 1.45-1.59(95% CI). Vascular mechanisms, direct neurotoxic elements in tobacco or oxydative stress?
- Former smoking was not associated with increased risk in most studies.

Cognitive Reserve

- Higher education/ occupation are associated to reduced risk of dementia and age-related cognitive decline
- Social networking, leisure activities (mental, physical social) protective
- However, higher education/ lifetime higher cognitive activities are associated with poorer outcome & more rapid decline in dementia patients…

APoE, Education, CV risk, leisure activities and AD Risk

Hazard ratios (HRs) and 95% confidence intervals (CIs) of dementia and Alzheimer's disease (AD) for the combined effect of APOE ε4 with education, vascular risk factors, or leisure activities (n = 932)

Joint exposure		No. of subject	Dementia (n = 323)		AD (n = 246)	
			n	HR (95% CI)[a]	n	HR (95% CI)[a]
Any ε4	Education					
+	Low	144	63	1.00 (Ref.)	51	1.00 (Ref.)
+	High	121	40	0.62 (0.41–0.96)	32	0.57 (0.36–0.92)
−	Low	383	141	0.75 (0.54–1.02)	110	0.67 (0.47–0.95)
−	High	284	80	0.46 (0.33–0.65)	54	0.36 (0.24–0.54)
Any ε4	Vascular risk factors					
+	Yes	102	50	1.00 (Ref.)	39	1.00 (Ref.)
+	No	163	53	0.60 (0.45–0.97)	44	0.64 (0.40–0.98)
−	Yes	282	101	0.82 (0.58–1.17)	62	0.64 (0.43–0.98)
−	No	385	120	0.55 (0.39–0.77)	102	0.54 (0.37–0.79)
Any ε4	Leisure activities score[b]					
+	Low	105	47	1.00 (Ref.)	37	1.00 (Ref.)
+	Moderate	75	35	1.06 (0.68–1.65)	29	1.07 (0.65–1.76)
+	High	83	20	0.53 (0.30–0.90)	16	0.51 (0.28–0.95)
−	Low	226	92	0.71 (0.41–1.23)	63	0.83 (0.44–1.55)
−	Moderate	205	65	0.48 (0.27–0.84)	54	0.55 (0.30–1.03)
−	High	225	62	0.44 (0.25–0.77)	46	0.56 (0.30–1.06)

[a] Adjusted for age, gender, BMI, surviving status, MMSE score, education, vascular risk factors, and leisure activities if applicable.

[b] Low score: low score in mental, physical, and social component; Moderate: scored as high in one or two of components; and High: high score in all three components. The number of subjects with missing values was 13 for leisure activity score.

Ferrari et al, 2012

Role of Education, leisure activities and vascular risk in AD Risk

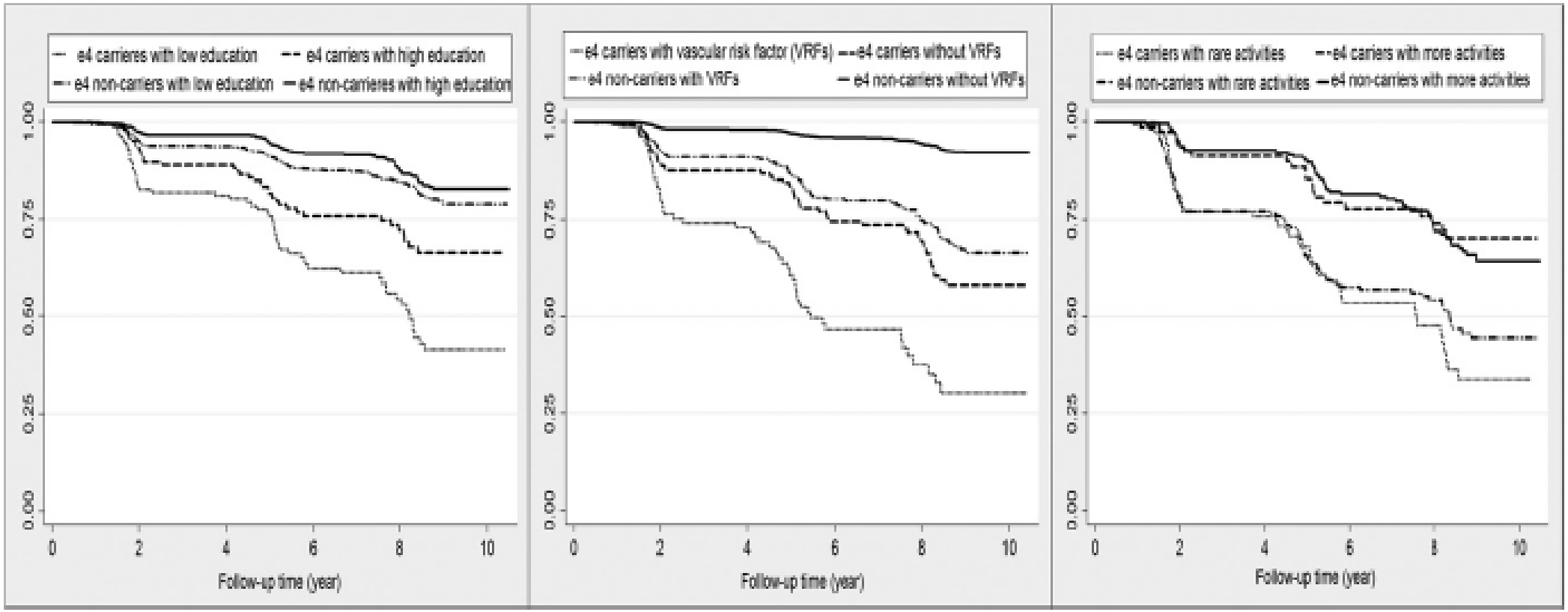

Fig. 1. Kaplan–Meier survival estimates from baseline to dementia occurrence by APOE ε4 in combination with education, vascular risk factors, and leisure activities (adjusted for age and sex). For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.

from Ferrari et al, 2012

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The environment
Risk and Protective Factors

Established AD Risk Factors

- Age > 65 years
- APoE4 and TOMM40- IVS6 polyT
- Diabetes increases risk 54%
- Mid-life obesity increases risk 59%
- Cerebrovascular disease and HTA
- Metabolic syndrome
- Head trauma
- Smoking
- Depression
- Stress?

Protective factors for AD

- Mediterranean Diet
- Physical activity
- Intellectual activity
- Social network/ activities
- APoE2 - TOMM40- short polyT

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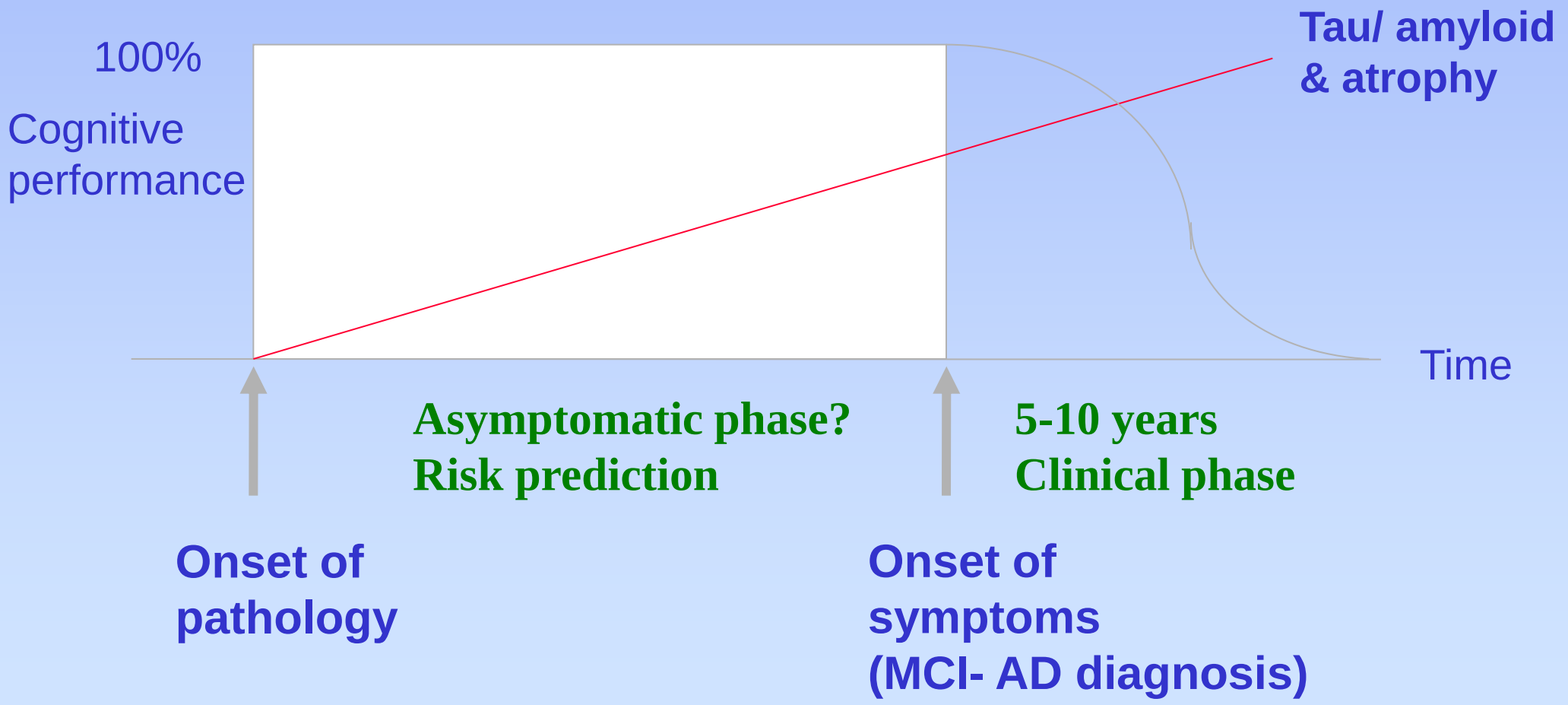
Theoretical disease pattern of cognitive decline in Alzheimer's disease



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Mechanistic Biomarkers reflecting progression of pre-AD to AD

[ADNI, Scandinavian groups and others, 2009/2011]

progression

Mechanism	Biomarkers
• **Pre symptomatic Upstream events**	• **CSFAβ1-42/ Aβ 1-40 reduced/ nl tau APoE4 carriers: PIB +ve & sMR**
• **MCI**	• **MRI- early signs of atrophy**
• **Early AD**	• **CSF T-tau, P-tau and ratio tau/ Aβ1-42 increased.**
• **AD (SP & NFT)**	• **CSF tau increased- CSF Aβ normalizes (?)**

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An Active Lifestyle Postpones Dementia Onset by More than One Year in Very Old Adults

Paillard-Borg S et al, 2012

- **Kungsholmen project**: In 1375 community dementia –free dwellers (mean age 81.2), over a 9 year period, there were 388 dementia cases.
- **17 months difference in AOO of dementia** between active and inactive groups, independent of education, medical condition(s), functional status and APoE

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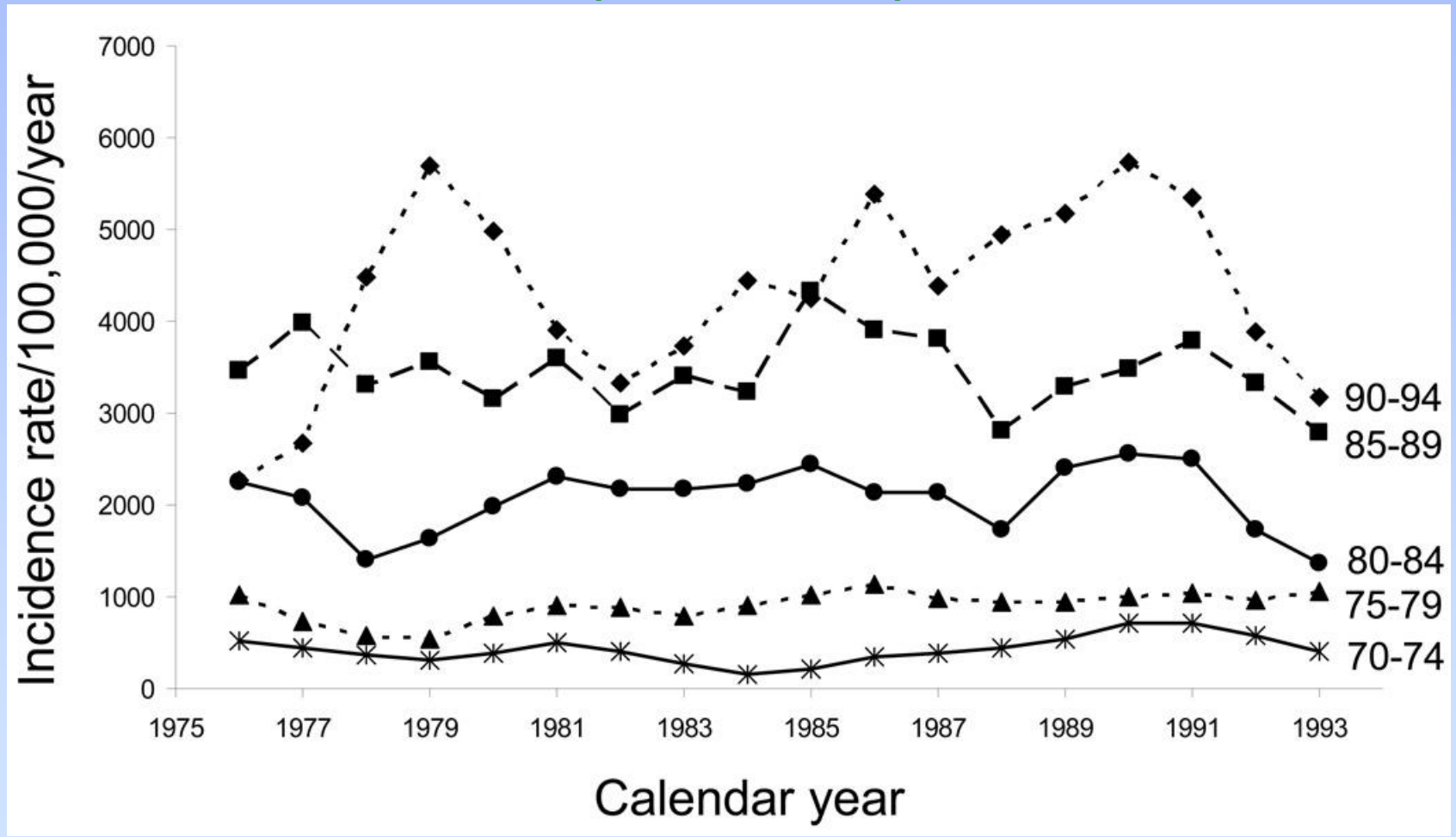
Time trends in age-specific incidence rates of Alzheimer's disease in men and women combined from 1975 through 1994 (moving 3-year average incidence rates per 100,000 person-years) In Rochester, Minnesota

(Rocca et al, 2011)



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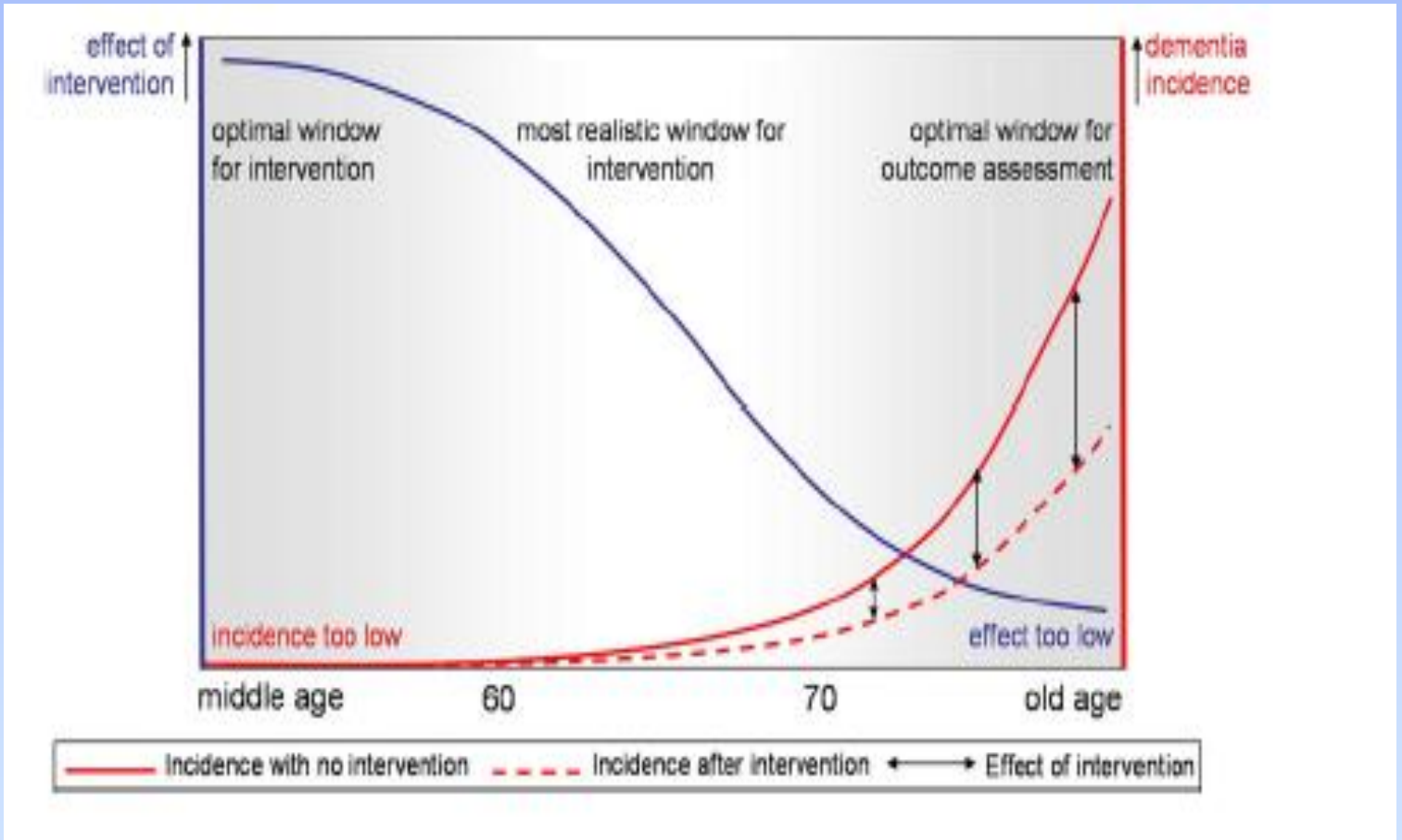
Optimal Time for Intervention



From Richard et al, 2012

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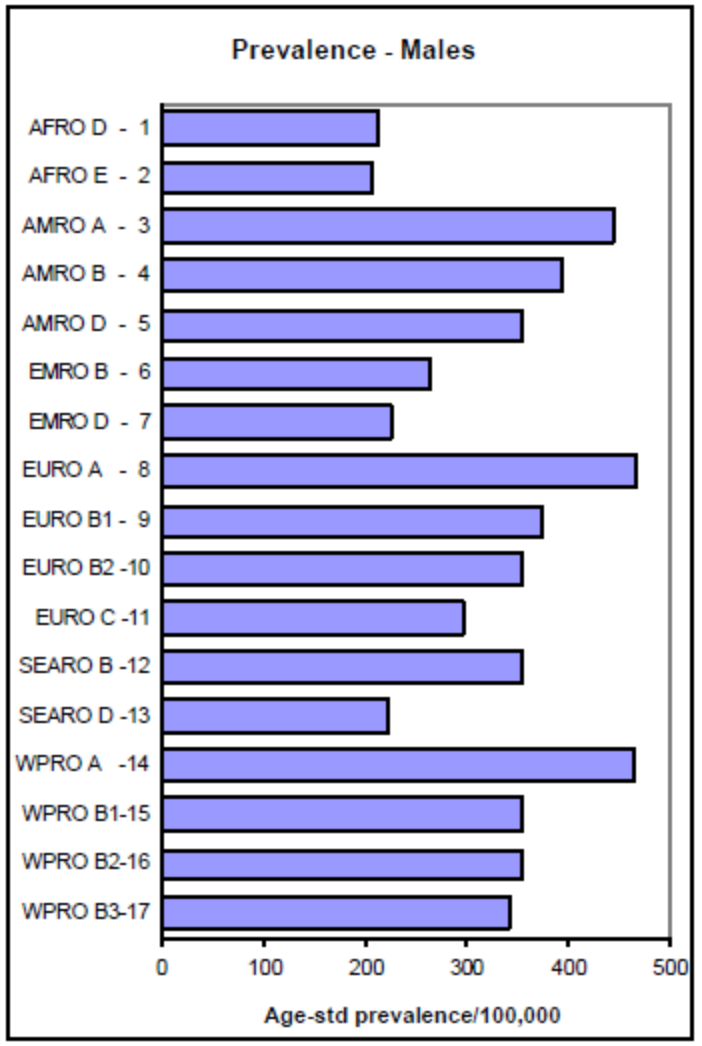
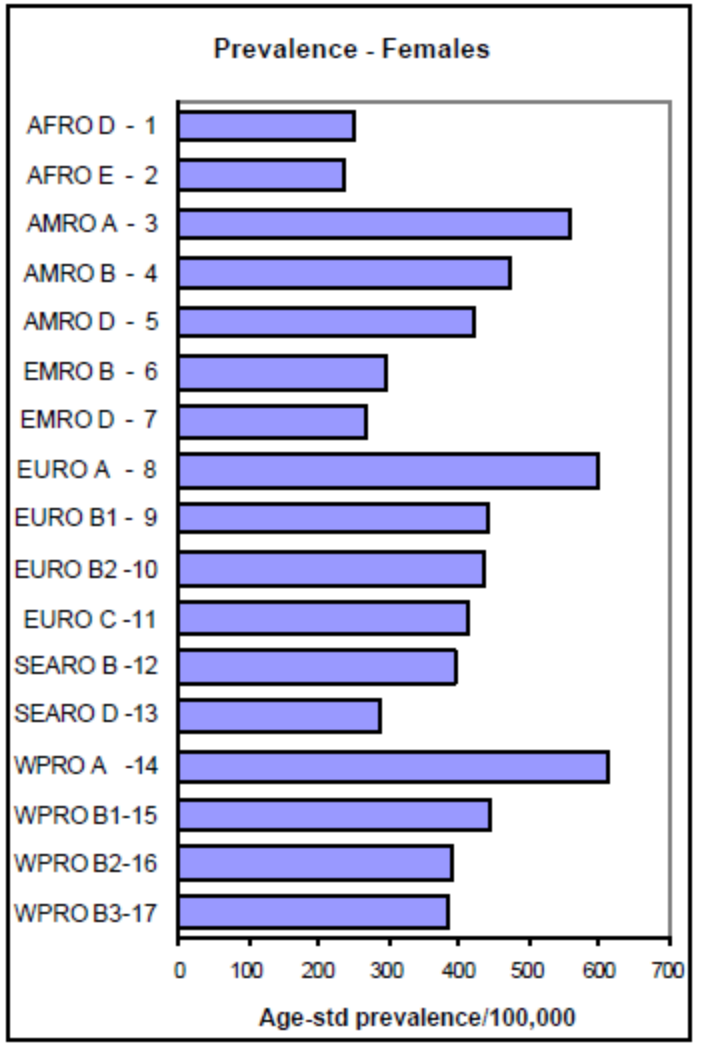




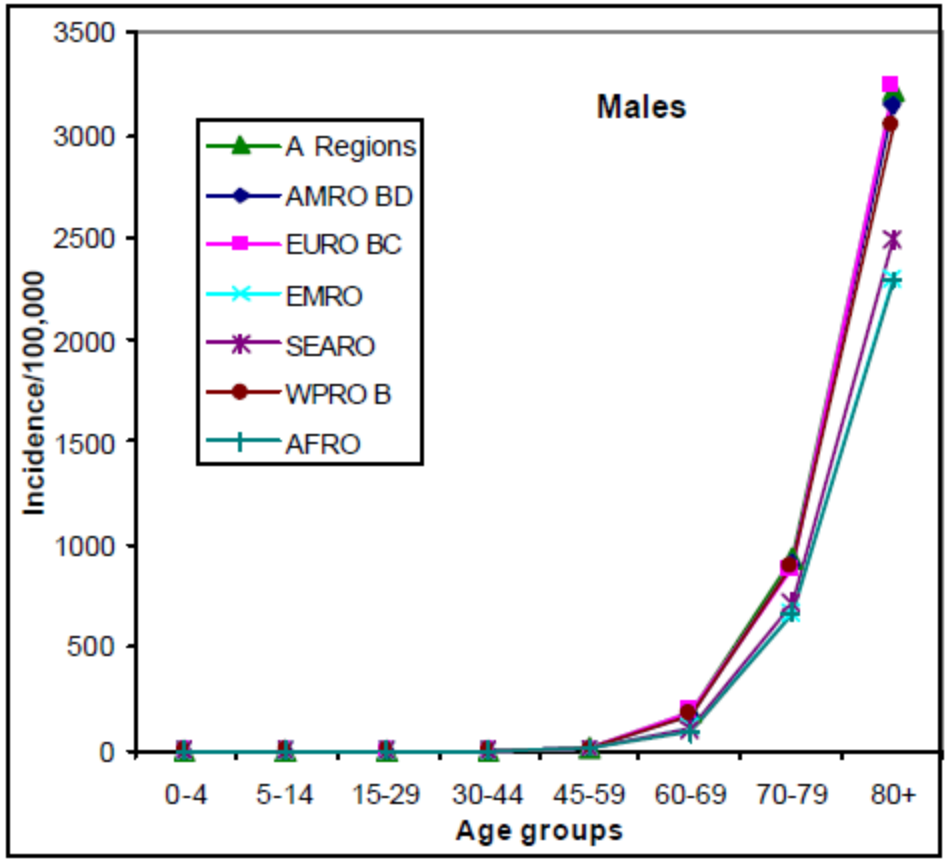
Global Burden of Disease 2000

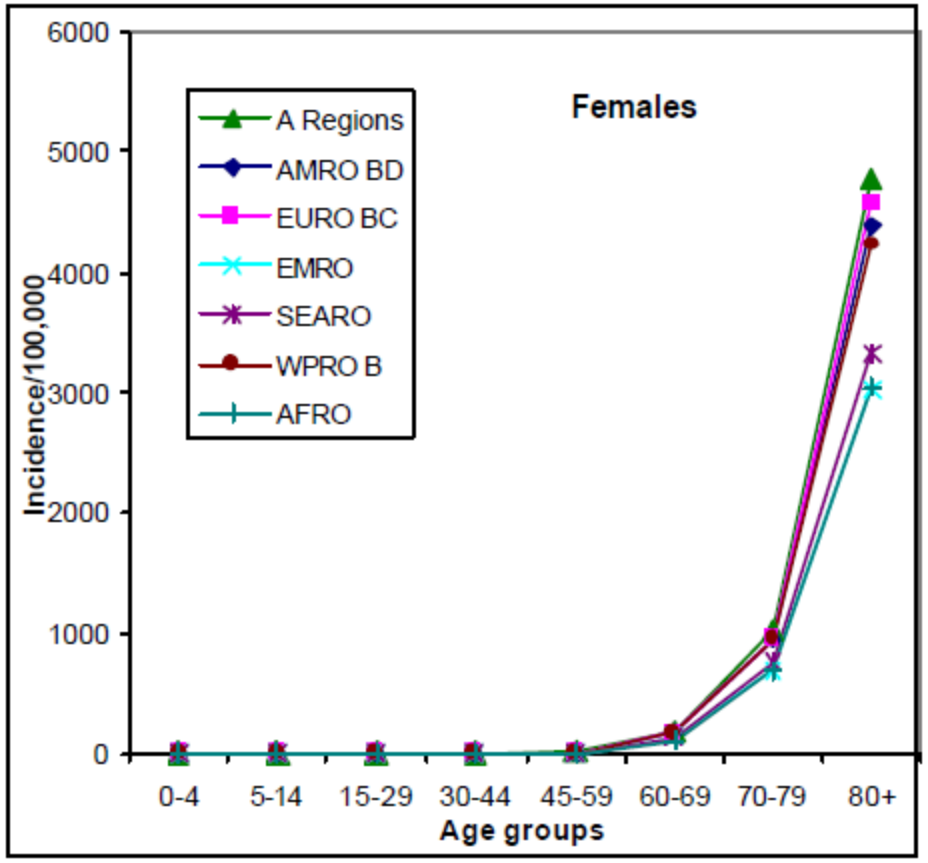
Table 1 | Prevalence and incidence of dementia in developed and developing regions

Region	Consensus dementia prevalence at age ≥60 years (%)	Estimated annual incidence of dementia (per 1,000 individuals)	People with dementia aged ≥60 years in 2001 (millions)	Estimated increase in proportion of people with dementia from 2001 to 2040 (%)
Western Europe	5.4	8.8	4.9	102
Eastern Europe (regions with low adult mortality)	3.8	7.7	1.0	169
Eastern Europe (regions with high adult mortality)	3.9	8.1	1.8	84
North America	6.4	10.5	3.4	172
Latin America	4.6	9.2	1.8	393
North Africa and Middle Eastern Crescent	3.6	7.6	1.0	385
Developed western Pacific	4.3	7.0	1.5	189
China and developing western Pacific	4.0	8.0	6.0	336
Indonesia, Thailand and Sri Lanka	2.7	5.9	0.6	325
India and south Asia	1.9	4.3	1.8	314
Africa	1.6	3.5	0.5	235
Combined values	3.9	7.5	24.3	234

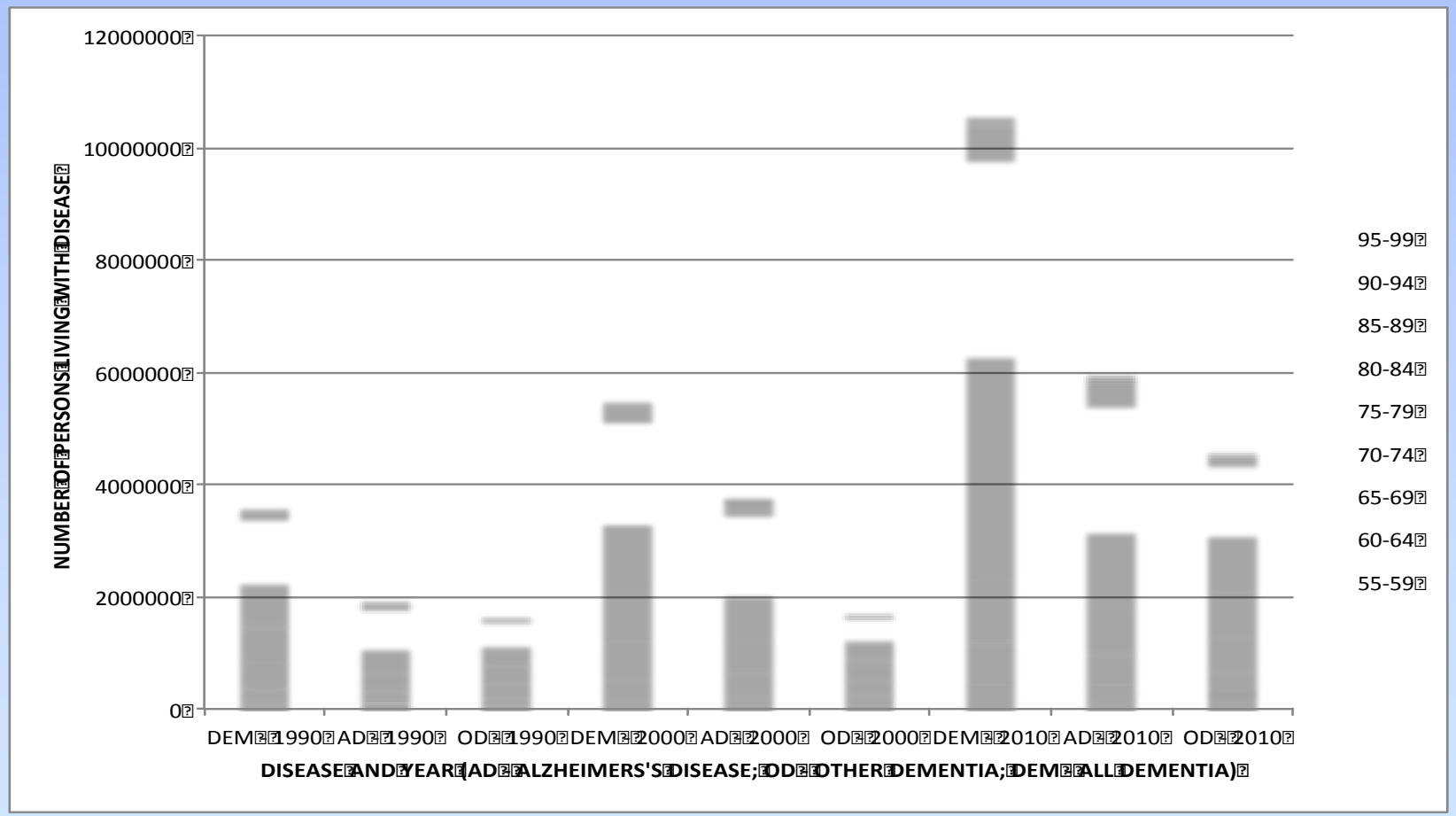
Data taken from Ferri *et al.* (2005).[3]

Figure 5.1 Age-specific dementia incidence rate estimates, WHO epidemiological subregions, by sex, 2000.





Predicted numbers of persons living with any form of dementia (DEM), Alzheimer's disease (AD) and other forms of dementia (OD) (e.g. vascular dementia, Lewy body dementia, fronto-temporal dementia and others) in China in 1990, 2000 and 2010 by contributing 5-year age groups.



Methodological Challenges in Epidemiological Studies in Late-onset Dementias

- Disease related:
  - Age of onset difficult to establish in many cases
  - Phenotypic overlaps between dementia sub-types
- Diagnostic methodologies
  - Variable diagnostic criteria
  - Variable neurocognitive assessment tools (education…)
    (memory vs social malfunction)
  - Variable levels of medical care
- Cultural/ social factors towards elderly
- Age distribution and mortality rates
- Lack of well designed prospective – population studies outside EU and USA

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I.A.R.C. - W.H.O.

EPIC European Prospective Investigation on Cancer and Chronic Diseases